REMARKS

Applicant respectfully requests reconsideration.

The specification has been amended to recite SEQ ID NO: 5 in the legend for Figure 1A.

Claims 1-57, 81, 95, 110-111, 122 and 146 were previously pending in this application. By this amendment, claims 57, 81, 95, 110-111, 122 and 146 are cancelled without prejudice or disclaimer. Claim 1 is amended. Support for this amendment can be found in the specification at least at paragraph [0074]. Claims 3, 5-29, 34, 35 and 41-51 have been withdrawn based on a species election. As a result, claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are pending for examination with claim 1 being an independent claim.

No new matter has been added.

Information Disclosure Statement

Applicant thanks the Examiner for the return of previously submitted 1449 Forms. However, the returned 1449 Form does not indicate the Examiner's consideration of Saxon et al. "Cell surface engineering by a modified Staudinger reaction", Science, 287:2007-2010, 2000. Applicant requests indication that the reference has been considered.

Objection to the Drawings

The drawings are objected to because there are no SEQ ID NOs. for the sequences in Figure 7. The figure legend for Figure 7 provides SEQ ID NOs: 1 and 2 respectively for the amino acid and nucleotide sequences in the Figure.

Accordingly, withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. §112

Written Description

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully traverses.

The claimed invention relates to a method for labeling a target protein. The method involves contacting a fusion protein with a biotin analog in the presence of a biotin ligase mutant

thereby allowing the biotin ligase mutant to conjugate the biotin analog to the fusion protein. The fusion protein is comprised of the target protein and an acceptor peptide.

The written description requirement is satisfied if a patent specification describes a claimed invention in sufficient detail that one of ordinary skill in the art could reasonably conclude that the inventor had possession of the claimed invention. (See Written Description Guidelines, Federal Register, Vol. 66, No. 4, January 5, 2001.) Possession can be shown by actual reduction to practice, a disclosure of drawings or chemical formulae, or a description of distinguishing identifying characteristics. Id. Whether a patent specification satisfies the written description requirement is an issue of fact that is determined on a case-by-case basis.

The Examiner states that "the claims do not recite any structure of the component methods such as fusion protein, biotin analog, and biotin ligase mutant". Applicant respectfully disagrees. The specification provides written description including structural and/or sequence characteristics for each claimed element as well as the claims as a whole. The specification discloses the "relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties" of the claimed genus and species thereof. It also provides "functional characteristics coupled with ... correlation between function and structure" of such claimed elements. Regents of University of Cal. v. Eli Lilly & Co. 119 F.3d 1559 (Fed. Cir. 1997). For example, the specification describes and provides examples of target proteins (see paragraphs [0012] and [0065]), acceptor peptides (see paragraphs [0013] and [0069]), and methods of conjugating the two (see paragraphs [0013], [0070] and [0071]).

The specification provides genus definitions as well as numerous species of biotin analogs and biotin ligase mutants. A biotin ligase mutant is defined as "a variant of biotin ligase that is enzymatically active towards a biotin analog". (See paragraph [0073].) Biotin ligase is BirA, the 321 amino acid sequence of which is provided as SEQ ID NO:1. The specification teaches that "the biotin ligase mutant can have various mutations, including addition, deletion or substitution or one or more amino acids" and that "preferably, the mutation will be present in the biotin interaction and activation region, spanning amino acids 83-235" but not at positions 1-26 or 183. (See paragraph [0074].) Thus, the genus of "biotin ligase mutants" comprises species with substantial sequence similarity. The specification further identifies residue positions 83, 89-91, 107, 112, 115-118, 123, 142, 186, 189, 190, 204, 206, 207 and 235 (relative to the wild type

biotin ligase amino acid sequence) as being particularly important for biotin interaction and affinity. A number of species of biotin ligase mutants is also provided including T90G, T90A, T90V, C107G, Q112M, G115A, Y132A, Y132G, S134G, V189G, I207S, T90G/N91S, T90G/N91G, T90A/N91A, T90A/N91A, T90A/N91L and T90V/N91L. Accordingly, based on the common characteristics within the genus, a representative number of species has been identified.

A biotin analog is defined as "a molecule that is structurally similar to biotin ... (and) ... that binds to a biotin ligase mutant in the interaction and activation domain". The analogs may share particular structural features with biotin such as an aliphatic carboxylic tail or a two ring structure and/or they may comprise a substitution at the trans ureido nitrogen. Examples of biotin analogs are provided in the specification (see paragraphs [0083] to [0093] for example) and chemical structures thereof are provided in Fig. 1B. The chemical structures demonstrate the similarity between biotin and biotin analogs, as well as between biotin analogs. Accordingly, a representative number of species of biotin analogs is also provided by the specification.

The specification further provides the structural correlations between biotin ligase mutants and their biotin analog substrates. (See paragraph [0154].) The specification demonstrates the ability of biotin ligase mutants to incorporate biotin analogs (as measured by inhibition of biotin incorporation). Table 1 shows that the T90G biotin ligase mutant is able to incorporate the N-ketone biotin analog and that the T90G/N91S biotin ligase mutant is able to incorporate both the N-ketone and N-alkyne biotin analog.

The Examiner cites Schatz (Biotechnology 1993 11:1138-1143) to challenge the ability to label a fusion protein since "changes in (biotinylated domains) as far as 33 or more residues from the modified K can abolish biotinylation". The reference however is directed at identifying consensus sequences of peptides that can be biotinylated by BirA biotin ligase. Accordingly, the reference supports rather than refutes the existence of peptides that can be attached to target proteins and subsequently biotinylated. The Examiner has even relied on patents deriving from this research (see 35 U.S.C. § 103(a) rejection) in the same Office Action. Thus, as evidenced by the art cited by the Examiner (in particular the Schatz literature reference and patents), acceptor peptides, their conjugation to target proteins, and their subsequent biotinylation were known in the art at the time of filing and thus are adequately described by the specification.

Accordingly, Applicant disagrees with the Examiner's assertion that the specification has described only one species encompassed by the genus and that the genus comprises substantial variation. The specification provides a representative number of species for each claim limitation and such number is sufficient to support each claimed genus.

The Examiner states that it is not clear that the claimed method has been reduced to practice. However, reduction to practice is not necessary for purposes of written description, particularly where the claimed invention is otherwise described. The Examiner goes on to state that "in biotechnological invention one cannot necessarily claim a genus after only describing a limited number of species. There may be unpredictability in the results obtained from species other than those specifically described." However, "[a]pplicants are not required to disclose every species encompassed by their claims, even in an unpredictable art". In re Robins, 429 F.2d 452, 456-57. While "[i]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group ... it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language'". The instant specification identifies the claimed genera, and it provides multiple examples of species within the genera. It therefore sufficiently describes the genus commensurate with the scope of the claims.

The Examiner cites Eli Lilly, Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002) (Enzo Biochem II), Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004), and In re Curtis, 354 F.3d 1347 (Fed. Cir. 2004) to support the rejection. As noted in Noelle, each case involving the issue of written description "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." Noelle, 355 F.3d at 1349 (citing Vas-Cath, 935 F.2d at 1562 (citing In re Driscoll, 562 F.2d 1245, 1250 (CCPA 1977)). Each of these cases can be factually distinguished from the instant case.

In Eli Lilly, claims to human insulin encoding genes were found not to be supported by a specification that disclosed only a single mouse insulin gene and provided no structural information for the claimed genus. The specification did not disclose any common distinguishing features possessed by the members of the genus. In Noelle, claims to a genus of antibodies to CD40CR were found not to be supported by a specification that described only mouse CD40CR and did not disclose any features shared by CD40CR from different species.

The instant specification, in contrast, describes features common to the genus, as described herein.

In Enzo Biochem II, the court reiterated its previous standard that "the written description requirement is satisfied by the patentee's disclosure of such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." Enzo Biochem II, 323 F.3d at 969, citing Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). The instant specification meets this standard by providing words, structures, figures and diagrams for the biotin analogs, biotin ligase mutants, acceptor peptides and target proteins of the claimed invention.

The court further stated that "the written description would be met for all the claims [of the claims at issue] if the functional characteristic of [the claimed invention was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Enzo Biochem II, 323 F.3d 956, 964 (Fed. Cir. 2002), citing the USPTO Written Description Guidelines, 66 Fed. Reg. at 1106. The instant specification is also consistent with this standard as it discloses a correlation between the structure of biotin analogs and the structure of biotin ligase mutants and their ability to interact with each other.

In In re Curtis, claims to dental floss coated with a genus of materials capable of increasing the coefficient of friction were not supported by a specification and a prosecution history of an earlier application that identified only one coating species as effective and further argued unpredictability in the genus of coatings in order to achieve patent protection of that single coating. The instant specification can be distinguished from that of Curtis by its disclosure of genera of biotin analogs and biotin ligase mutants and the illustrated commonality between species of either genus, as described herein.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, written description, is respectfully requested.

Enablement

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses.

The enablement requirement is satisfied if one of ordinary skill in the art is able to make and use the claimed invention without undue experimentation, based on the specification and the knowledge in the art at the time of filing. The experimentation required to make and use the claimed invention may be complex, and still not undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive. The analysis of these factors as presented below illustrates that the experimentation required to practice the invention is not undue, and thus the specification enables the claimed invention.

Nature of the Invention: The claimed invention is premised on the finding that the strict fidelity of wild type biotin ligase for biotin can be eased to create variants of biotin ligase that have a relaxed substrate specificity that includes specificity for biotin analogs, optionally to the exclusion of biotin.

Breadth of the Claims: The claimed invention relates to a method for labeling a target protein by contacting a fusion protein comprised of the target protein and an acceptor peptide with a biotin analog in the presence of a biotin ligase mutant. The Examiner states that the biotin analog, biotin ligase mutant, the acceptor peptide and the target protein all encompass a "large diversity". As outlined above, each of these terms is structurally and functionally defined in the specification and examples of each are provided in the specification. The sequences of various biotin ligase mutants are provided as are the chemical structures of various biotin analogs. The sequences of various acceptor peptides are also provided. The target protein can be any protein which can be conjugated to the acceptor peptide either at the nucleic acid or amino acid level.

State of the Art: The state of the art is exemplified by the Schatz reference and patents cited to and from the Examiner. (See for example U.S. Patent Nos. 5,723,584, 5,874,239, 5,932,433 and 6,265,552.) The art was familiar with the ability to exploit the specificity of wild type biotin ligase in order to biotinylate a target protein for the purpose of labeling and

monitoring such protein. The art had identified consensus sequences for acceptor peptides that are biotinylated by biotin ligase, and fusion of the acceptor peptide to a target of interest was routine. The Examiner states that "techniques or methods are specifically applied or adapted for a known or defined structure of a specific acceptor peptide and biotin present in a specific prokaryote or eukaryote". Applicant disagrees. The Schatz patents of record clearly demonstrate a number of acceptor peptides that can be fused to *any* target protein, thereby allowing such protein to be biotinylated by biotin ligase. The Schatz patents demonstrate the specificity that biotin ligase has for such acceptor peptides and thus the specificity of biotinylation of *any* fusion proteins that comprise the acceptor peptide provided biotin ligase is present.

Level of Ordinary Skill in the Art: The level of ordinary skill in the art is also exemplified by the Schatz patents of record. The ordinary artisan would be familiar with, inter alia, isolation and mutation of biotin ligase genes and proteins, synthesis of fusion proteins at either the nucleic acid or amino acid level, and biotinylation assays.

Amount of Direction Provided by the Inventor: The specification provides definitions, sequence and/or structural information, and examples of biotin ligase mutants, biotin analogs acceptor peptides, and target proteins. The sequence of wild type biotin ligase was known, and the specification provides sufficient guidance regarding the location and nature of mutations as well as numerous examples of biotin ligase mutants. The synthesis of such mutants would have been routine based on the sequences provided in the specification. The specification also provides the structure of a number of biotin analogs as well as guidance as to how to make such analogs. (See Figs. 1B, 4 and 5.) The acceptor peptide sequences and functions were also known as was the ability to conjugate them to any target protein. The Examiner doubts the range of proteins that can be labeled with the biotin analogs and biotin ligase mutants of the invention. As disclosed in the specification and in the Schatz patents of record, virtually any protein can be labeled provided it comprises the acceptor peptide. As taught in the specification, the biotin interaction and activation domain is located at amino acid residues 83-235 and is physically separate from the acceptor peptide binding site located within amino acid residues 1-26.

Level of Predictability in the Art: The level of predictability in the art is also exemplified by the Schatz patents of record. The use of wild type biotin ligase and biotin to biotinylate a

target protein that is conjugated to an acceptor peptide was established in the art at the time of filing. The claimed invention relates to the use of a *biotin ligase mutant* that is able to recognize and conjugate a *biotin analog* to an acceptor peptide that is conjugated to a target protein. The specification demonstrates the incorporation of biotin analogs in the presence of biotin ligase mutants. (See Table 1.)

Working Examples: The Examiner states that the specification fails to provide working examples. Applicant disagrees and points the Examiner to Table 1 which demonstrates the incorporation of biotin analogs using biotin ligase mutants to the complete or partial exclusion of biotin incorporation. Notwithstanding these data, however, the claimed invention is enabled by the specification since the courts have previously held that a specification need not contain a working example if the disclosure of the invention is adequate to allow one of ordinary skill to practice it without undue experimentation (i.e., if the disclosure is otherwise enabling). In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970).

Quantity of experimentation needed to practice the invention: In view of the teaching of the instant application and the state of the art at the time of filing, Applicant submits that the claimed invention can be practiced without undue experimentation.

Finally, the Examiner states that one of the undefined variables of the claimed method is the microorganism and/or eukaryote containing biotin. The method does not require a microorganism or eukaryote as a source of biotin. Rather the method contemplates the addition of exogenous *biotin analog* to a labeling system. Applicant requests clarification.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, enablement, is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 1, 2, 4, 30-33, 35, 37-38 and 53-56 are rejected under 35 U.S.C. §103(a) as being unpatentable over Schatz et al. in view of Oh et al. (U.S. Patent No. 5,168,057) or Huber et al. (U.S. Patent No. 5,952,185). The Examiner has not identified the Schatz reference, however, according to the citation, Applicant assumes it to be U.S. Patent No. 5,932,433 (which has a specification identical to that of U.S. Patent Nos. 5,723,584 and 6,265,552). If this is incorrect, Applicant requests clarification.

Schatz teaches biotinylation of a fusion protein using a wild type biotinylation enzyme such as BirA. The reference does not contemplate mutant biotinylation enzymes or their use in labeling fusion proteins with compounds other than biotin. Oh and Huber provide biotin containing derivatives. These references do not contemplate mutant biotin ligases either. Thus, even if appropriate, the combination of references does not result in all the limitations of the pending claims, all of which at a minimum require a mutant biotin ligase.

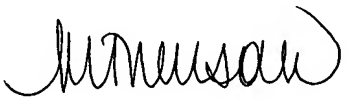
Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



Maria A. Trevisan, Reg. No. 48,207
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000

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